

SUPPLEMENTARY FILE 1

3+3 dose-escalation schedule and inpatient dose-escalation

Maximum administered dose

If 0/3 patients exhibit dose-limiting toxicity at this dose level:

- Dose escalation to the next dose level may begin in a new cohort of patients
- Patients enrolled on the previous dose level who are still receiving therapy may now undergo inpatient dose escalation to this new dose level provided that they have experienced no drug related toxicity of grade 2 or higher at the previous dose level.

If 1/3 patients exhibit dose-limiting toxicity at this dose level:

- Expand dose level to a total of six patients. Toxicity information from patients who underwent inpatient dose escalation can be used for expansion cohorts, but only when they have completed at least 8 weeks of treatment at the new dose level.
- If no further DLT events are observed, dose escalation to the next dose level may begin in a new cohort of patients and patients enrolled on the previous dose level who are still receiving therapy may now undergo inpatient dose escalation to this dose level provided that they have experienced no drug related toxicity of grade 2 or higher.
- If further DLTs are observed (i.e. in $\geq 2/6$ patients), this dose level will be considered the maximum administered dose (MAD).

If $\geq 2/3$ patients exhibit dose-limiting toxicity

- This dose level will be considered the MAD.
- If this toxicity occurs at level 1 (starting level), dose de-escalation to level -1 will be applied.

Recommended phase II dose

As described in the full text manuscript, the MAD is the dose in which $\geq 2/3$ or $\geq 2/6$ patients experience a DLT, or the final dose from the dose escalation schedule (1500 mg metformin b.i.d. and 200 mg chloroquine q.d.). One dose level below the MAD will be considered the RD for follow-up phase II clinical trials. When the starting dose level ("1") is the MAD, we will de-escalate the dose level to dose level "-1". When we do not observe DLTs in three patients or one DLT in six patients at this dose level, then dose level "-1" will be the RD. When we observe more than one DLT, the combination of metformin and chloroquine will be considered too toxic to be useful in cancer patients. In contrast to this situation where we have to accept the lowest dose-escalation level as the RD, when 0/6 patients experience DLTs at the final dose level of the dose escalation schedule (i.e. dose level "3"), this can be considered the RD for follow-up phase II clinical trials, instead of dose level "2".

Up to a total of six patients may be treated at the RD level to assure information on the safety profile when that dose is complete. When clinically appropriate, intermediate dose levels may be studied to assure that the RD is the highest tolerable. Furthermore, when pharmacokinetic data suggests that saturating absorption of drug is occurring on a b.i.d. oral administration

level, further dose splitting to three times a day or four times a day schedules may be considered.

Patient replacement

Three patients within a dose level must be observed for eight weeks before accrual to the next dose level may begin. If a patient is withdrawn from the study prior to completing 22 days of therapy without experiencing a DLT prior to withdrawal, an additional patient may be added to that dose level. Patients missing seven or more doses (one week) due to toxicity will not be replaced since these patients will be considered to have experienced a dose-limiting toxicity.

Data monitoring

Based on the guideline by the NFU (Dutch Federation of University Medical Centers) about quality insurance in human research (“Kwaliteitsborging van mensgebonden onderzoek”) and the “Risk assessment in clinical research projects regarding the required management and monitoring strategy” by the AMC Clinical Research Unit, the risk of this study was qualified as ‘moderate’.

According to this moderate risk a ‘minimal intensive monitoring’ is advised, which will be performed by an independent clinical research and consists of:

- 1 visit per year, per center
- 1-10% of patient cases will be checked for informed consent
- First 3 patients per center will be checked on in/exclusion criteria, then 1-10% of patients thereafter
- 1-10% of patient cases will be checked for Source Data Verification
- 1-10% of patients will be checked for SAEs (serious adverse events) and SADR (serious adverse drug reactions)